

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|---|----------|
| 176 tcttgacgttccccggcggtccccgtgcgt | o |
| 177 tctgtgcgtcctgtgcgtcctgtgcgt | o |
| 178 tctggcggggaagt | o |
| 179 tctgaggttgaagt | o |
| 180 tctgacgttgaagt | o |
| 181 tctagcgttgaagt | o |
| 182 tccagacgttgaagt | o |
| 183 tctgacggggaagt | o |
| 184 tctggcggtgaagt | o |
| 185 ggctccggggagggaattttgtctat | o |
| 186 atagacaaaaattccccccggagcc | o |
| 187 tccatgagcttcttgagtct | rna |
| 188 tctgcgtgtctccgcttctt | so |
| 189 tctgcgtgtctccgcttctt <i>regtcgcgttcgcttctt</i> | s20 |
| 190 tctgagcattgcacatcatctg | o |
| 191 cagatttgtcaatgtctcga | o |
| 192 tccatgtcgttctctgatgcg | o |
| 193 gcgatgtcgttctctgatgct | o |
| 194 gcgatgtcgttctctgatgcg | o |
| 195 tccatgtcgttccgcgcgcg | o |
| 196 tccatgtcgttctctgcgcgt | o |
| 197 tccatgtcgttctctgtagct | o |
| 198 gcggcgggcggcgcgcgcgc | o |
| 199 atcaggaaacgtcatgggaagc | o |
| 200 tccatgagcttctctgagtct | p-ethoxy |
| 201 tcaacgtt | p-ethoxy |
| 202 tcaagctt | p-ethoxy |
| 203 tctgtcgttctctgtcgtt | s |
| 204 tccatgtcgtttttgtcgtt | s |
| 205 tctgtcgttctctgtcgtt | s |
| 206 tctgtcgttctctgtcgtt | s |
| 207 btccattccatgacgttctctgatctcca | os |
| 208 tctgtcgtttttgtcgtt | s |
| 209 tctgcgtgtctccgcttctt | s |
| 210 tctgcgtgtctccgcttctt | s |
| 211 tctgcgtgttgcgtttctt | s |
| 212 tctgtcgttctctgcgttggaaacgacag | o |
| 213 tctgtcgttctctgcgtttcaacgtcaggaaacgacagga | o |
| 214 ggggtctcgttttgggggg | sos |
| 215 ggggtctcgttttgggggg | sos |
| 216 tccggccgttgaagt | o |
| 217 tccggacgttgaagt | o |
| 218 tccggccgttgaagt | o |
| 219 tccagacgttgaagt | o |
| 220 tccggacgttgaagt | o |
| 221 tccagacgttgaagt | o |
| 222 tccatgtzgttctctgtzgtt | s |
| 223 tccatgacgttctctgacgtt | sos |
| 224 ggggttgacgttttgggggg | sos |
| 225 tccaggacttctctcaggtt | s |
| 226 ttttttttttttttttttt | s |
| 227 tccatgccgttctctgccgtt | s |
| 228 tccatggcgggcctggcggtt | s |
| 229 tccatgacgttctctgccgtt | s |
| 230 tccatgacgttctctggcggtt | s |
| 231 tccatgacgttctctgccgtt | s |
| 232 tccatgacgttctctgacgtt | s |
| 233 tccatgcgttgcgttgcgtt | s |
| 234 tccatgcgttgcgttgcgtt | s |
| 235 btccattccattctagccctgagcttccat | os |
| 236 tccatgacgttctctgacgtt | o |
| 237 tccatgtcgttctctgtcgtt | o |
| 238 tccatgacgttctctgacgtt | o |
| 239 tccattgcgttctctgcgtt | o |
| 240 tccatgacgttctctgacgtt | o |
| 241 tccatgatttctctgcgttctctgattt | o |
| 242 tccatgacgttctctgacgtt | s |
| 243 ggcggcggtggcgggcggt | o |
| 244 tccagacgttctctgacgtt | s |
| 245 tctgcgttgcgttgcgtt | s |
| 246 tctgcgttgcgttgcgtt | s |
| 247 tctgcgttgcgttgcgtt | s |
| 248 gcgtgcgttgcgttgcgtt | s |
| 249 czggcgzggcgzggcgzggcg | o |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|---|----------|
| 250 ggggggggggggggggggggg | S |
| 251 agicccgigaacgiattcac | O |
| 252 tgtcggttgctggttgctggt | S |
| 253 tgtcggttgctggttgctggt | S |
| 254 tgtcggttgctggttgctggt | S |
| 255 tgcgtgtgctggt | S |
| 256 tgtcggttgctggt | S |
| 257 cccccccccccccccccccc | S |
| 258 tctagcggttttagcggtcc | SOS |
| 259 tgcacccccagggccaccat | S |
| 260 tgcgtcgctgctgctgctgctg | SOS |
| 261 tgcgtcggttgctggttgctg | SOS |
| 262 tgcgtcggttgctggttgctg | SOS |
| 263 tgcgtcggttgctggttgctg | SOS |
| 264 ggggagggaggaactctttaaattccccagaatggtt | O |
| 265 aaacattctgggggaattttaagaagtctctccctcccc | O |
| 266 atgtttactctttaaattccccagaatggtt | O |
| 267 aaacattctgggggaattttaagaagttaaacat | O |
| 268 atgtttactagacaaaattccccagaatggtt | O |
| 269 aaacattctgggggaattttgtctagtaaacat | O |
| 270 aaaaattgacgttttaaaaaa | SOS |
| 271 ccccttgacgttttcccccc | SOS |
| 272 ttttcggttggttttgctggt | |
| 273 tgcgtcggttgctggttttgctggt | SOS |
| 274 ctgcagccctgggac | O |
| 275 acccgtcgtaattatagtaaaacc | O |
| 276 ggtacctgtggggacattgtg | O |
| 277 agcacccgaacgtgagagg | O |
| 278 tccatgccgttctctccggtt | O |
| 279 tccatgacggtctctgaggg | O |
| 280 tccatgccggtctctgaggg | O |
| 281 tccatgcgcgtctctgcggt | O |
| 282 ctgggtctttctgggtttttctgg | S |
| 283 tcagggggtgggggaacctt | SOS |
| 284 tccatgaggttctctagttct | O |
| 285 tccatgatgttctctagttct | O |
| 286 cccgaagtcatctctcttaacctgg | O |
| 287 ccagggttaagaggaaatgaactcggg | O |
| 288 tccctggzgggggaagt | O |
| 289 gzzggzggggzggzggzggcc | X |
| 290 tccatgtgcttctctgatgct | O |
| 291 tccatgtccttctctgatgct | |
| 292 tccatgtcgttctctagttct | |
| 293 tccaaagttagttctctagttct | O |
| 294 tccatgtagttctctagttct | O |
| 295 tcccgcgcgttccgcgcgtt | S |
| 296 tccctggcgggtcctggcgggt | S |
| 297 tccctggaggggaagt | O |
| 298 tccctgggggggaagt | O |
| 299 tccctggtgggggaagt | O |
| 300 tgcgtggttgctggttttgctggt | O |
| 301 ctggtctttctgggtttttctgg | O |
| 302 tccatgacgttctctgacgtt | |
| 303 tccaggacttctctcaggtt | SOS |
| 304 tzgtzgtttgtzgtttgtzgtt | O |
| 305 bctgctggttctgctggtttgtcgttttttt | OS |
| 306 gctatgacgttccaagg | S |
| 307 tcaacgtt | S |
| 308 tccaggacttctctcaggtt | O |
| 309 ctctctgtaggcccgcttg | S |
| 310 ctctcgttggaaccttggt | S |
| 311 gtccgggccaaggccaaagtc | S |
| 312 gtgcgcgcgagccgaaatc | S |
| 313 tccatgaigtctctgaigt | S |
| 314 aatagtcgcataaacaac | O |
| 315 aatagtcgcataaacaac | O |
| 316 btttttccatgtcgttctctgatgcttttt | OS |
| 317 tccctgctggtgaagttttt | O |
| 318 gctagcttttagagcttttagagctt | O |
| 319 tgcgtgcttcccccccccc | O |
| 320 tgcaggttcccccccccc | O |
| 321 tgcgtgcttcccccccccc | O |
| 322 tgcgtgcttcccccccccc | O |
| 323 tgcaggttcccccccccc | O |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|---|----------|
| 324 tcgtcgatccccccccccc | o |
| 325 tcctgacgttgaagt | s |
| 326 tcctgccgttgaagt | s |
| 327 tcctgacgttgaagt | s |
| 328 tctgagcttgaagt | s |
| 329 tcctggcggggaagt | s |
| 330 aaaaatctgtgtttttaaaaa | sos |
| 331 gatccagtcacagtgacctggcagaatctggat | o |
| 332 gatccagattctgccaggtcactgtgactggat | o |
| 333 gatccagtcacagtgactcagaagaatctggat | o |
| 334 gatccagattctgtcgagtcactgtgactggat | o |
| 335 tcgtcggtccccccczzccc | o |
| 336 tzgtcggtccccccccccc | o |
| 337 tzgtcggtccccccccccc | o |
| 338 tcgtzgttccccccccccc | o |
| 339 tcgtcggtccccccccccc | o |
| 340 tcgtcggtccccccccccc | o |
| 341 tcggcggtccccccccccc | o |
| 342 ggccctttccccccccccc | o |
| 343 tcgtcggtttgacgttttgcgtt | s |
| 344 tcgtcggtttgacgttttgcgtt | s |
| 345 ccgtcggtccccccccccc | o |
| 346 gcgtcggtccccccccccc | o |
| 347 tcgtcattcccccccgcccc | o |
| 348 acgtcggtcccccccgcccc | o |
| 349 ctgtcggtccccccccccc | o |
| 350 btttttcgtcggtccccccccccc | os |
| 351 tcgtcggtcccccccccccb | o |
| 352 tcgtcggtttgtcggtttgtcggtb | o |
| 353 tccagttccttcctcagtt | o |
| 354 tzgtcggtttgtcggtttgtcggt | o |
| 355 tcctggaggggaagt | s |
| 356 tcctgaaaaggaagt | s |
| 357 tcgtcggtccccccccccc | s |
| 358 tzgtzgtttgtzgtttgtzgtt | s |
| 359 ggggtcaagcttgagggggg | sos |
| 360 tgctgcttccccccccccc | s |
| 361 tcgtcggtcggtt | s2 |
| 362 tcgtcggtcggtt | s20 |
| 363 tcgtcggtcggtt | os2 |
| 364 tcaacgttga | s |
| 365 tcaacgtt | s |
| 366 atagttttccatttttttac | |
| 367 aatagtcgccatcgcgagac | o |
| 368 aatagtcgccatccccggac | o |
| 369 aatagtcgccatccccccc | o |
| 370 tgctgctttgtgctttgtgctt | o |
| 371 ctgtgctttctgtgtttttctgtg | s |
| 372 ctaatctttctaatttttttctaa | s |
| 373 tcgtcggttggtgtcggttggtcggt | s |
| 374 tcgtcggttggtgtcggttttggt | s |
| 375 accatggagcagctgtttcccttc | |
| 376 tcgtcggtttgtcggtcggtt | s |
| 377 ctgttaagtgaagcttgagag | |
| 378 gagaacgctggaccttc | |
| 379 cgggcgactcagtcctatcgg | |
| 380 gttctcagataaagcggaaccagcaacagacacagaa | |
| 381 ttctgtgtctgttgctggttcgctttatctgagaac | |
| 382 cagacacagaagcccgatagacg | |
| 383 agacagacacgaacgaccg | s |
| 384 gtctgtcccatgatctcgaa | |
| 385 gctggccagcttacctccc | |
| 386 ggggcctctatacaacctggg | |
| 387 ggggtccctgagactgcc | |
| 388 gagaacgctggaccttcct | |
| 389 tccatgtcggtcctgatgct | |
| 390 ctcttgccgacctggaaggta | |
| 391 aggtacagccaggactacga | |
| 392 accatggacagactgtttcccttc | |
| 393 accatggattacctttttccctt | |
| 394 atggaaggctccagcgttctc | o |
| 395 agcatcaggaccgacatgga | o |
| 396 ctctccaaagctcacttacag | |
| 397 tccttgagactgccccacctt | |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|--|----------|
| 471 tcagctctggtaactttttca | |
| 472 tgggttacgggtctgtcccatg | |
| 473 gtctatcggaggaactggcg | |
| 474 cattttacggggcgggcg | |
| 475 gaggggacattttacgggc | |
| 476 tgtccagccgaggggacat | |
| 477 cgggcttacggcggtgctg | |
| 478 tggaccttctatgtcggtcc | |
| 479 tgtcccatgttttagaage | |
| 480 gtgggttacgggtcgtgccc | |
| 481 cctccaaatgaagaccccc | |
| 482 ttgtactctccatgatggtt | |
| 483 ttccatgctgtccggctgg | |
| 484 gaccttctatgtcggtcctg | |
| 485 gagaccgctcgaccttcgat | |
| 486 ttgccccatatttttagaaac | |
| 487 ttgaaactgaggtgggac | |
| 488 ctatcggaggactggcgccg | |
| 489 ctgggagggcctccggcg | |
| 490 gctgaaccttccatgctgtt | |
| 491 tagaaacagcattctcttttagggcagcaca | |
| 492 agatgggttctcagataaagcggaa | |
| 493 ttccgctttatctgagaaccatct | |
| 494 gtcccagggtgtatagagctgc | |
| 495 gcgccagtcctccgatagac | |
| 496 atcggaggactggcgccg | |
| 497 ggtctgtcccatatttttag | SOS |
| 498 tttttcaacgttgagggggg | SOS |
| 499 †ttttcaacgttgattttt | SOS |
| 500 ggggtcaacgttgattttt | SOS |
| 501 ggggttttcaacgttttgagggggg | SOS SOS |
| 502 ggttacgggtctgtcccatat | |
| 503 ctgtcccatatttttagaca | |
| 504 accatcctgaggccattcgg | |
| 505 cgtctatcgggcttctgtgtctg | |
| 506 ggccatcccacattgaaagt | |
| 507 ccaaatatcggtggcgaagcac | |
| 508 gtgcttgaccaccgatatttg | |
| 509 gtgctgatcccgatatcctgttcgg | |
| 510 ggccaaacttcaatgtgggatggcctc | |
| 511 ttccgcgaatggcctcaggaatgggtac | |
| 512 tatagtccctgagactgccccaccttctcaacaacc | |
| 513 gcagcctctatacaacctgggacggga | |
| 514 ctatcggaggactggcgccg | |
| 515 tatcggaggactggcgccg | |
| 516 gatcggaggactggcgccg | |
| 517 ccgaacaggatcgggtgatcagcac | |
| 518 ttttggggtcaacgttgagggggg | |
| 519 ggggtcaacgttgagggggg | SOS |
| 520 cgccgcgcgcgcgcgcgcg | S |
| 521 ggggcatgacgttcggggggg | SS |
| 522 ggggcatgacgttcaaaaaa | S |
| 523 ggggcatgacgttcggggggg | S |
| 524 ggggcatgacgttcggggggg | SOS |
| 525 aaaaacatgacgttcaaaaaa | SOS |
| 526 aaaaacatgacgttcggggggg | SOS |
| 527 ggggcatgacgttcaaaaaa | SOS |
| 528 accatggagcatctgtttccctc | S |
| 529 gccatggagcaactgtttccctc | S |
| 530 ccccccccccccccccc | SOS |
| 531 gggggggggggggggggggg | SOS |
| 532 gctgtaaaatgaatcgccg | SOS |
| 533 ttccggcggaactcctccatt | SOS |
| 534 tatgcgcgcgcggacttat | SOS |
| 535 ggggtaatcgatcagggggg | SOS |
| 536 tttgagaacgtggaccttc | SOS |
| 537 gatcgtgatctaagtctcg | SOS |
| 538 gtcggtcctgatgctgttc | SOS |
| 539 tcgtcgtcagttcgtgtcg | SOS |
| 540 ctggaccttccatgtcgg | SOS |
| 541 gctcgttcagcgcgtct | SOS |
| 542 ctggaccttccatgtc | SOS |
| 543 caactgtccttcgtcga | SOS |
| 544 cgtggaccttccatgtcgg | SOS |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|--|----------|
| 545 gctgagctcatgccgtctgc | sos |
| 546 aacgctggaccttccatgtc | sos |
| 547 tgcattgccgtacacagctct | sos |
| 548 ccttccatgtcggctcctgat | sos |
| 549 tactcttcggatcccttgcg | sos |
| 550 ttccatgtcggctcctgat | sos |
| 551 ctgattgctctctcgtga | sos |
| 552 gggcgcttatctcgtactgcc | o |
| 553 cctacgcttgatgcgcccagct | o |
| 554 ggggtaatcgatgagggggg | o |
| 555 ttccggcggactcctccatt | o |
| 556 ttttttttttttttttttt | o |
| 557 gggggtttttttttggggg | o |
| 558 tttttgggggggggttttt | o |
| 559 ggggggggggggggggggt | o |
| 560 aaaaaaaaaaaaaaaaaaaa | o |
| 561 cccccccccccccccccc | o |
| 562 aaaaacccccccccccaaa | o |
| 563 ttgaaattcaggactggtaggtgag | o |
| 564 ttgaaattcctcagcggctcctcagtggc | o |
| 565 aattctctatcggggcttctgtgtctgttgcgttccgctttat | o |
| 566 ctagataaagcggaaccagcaacagacacagaagccccgatagag | o |
| 567 tttctagagaggtgcacaatgctctgg | o |
| 568 ttgaaattcctgtgtacagaagcgagaagc | o |
| 569 ttgcccgcgttagacttaa ^g ctgagagata ^e | o |
| 570 ttggggccacgagagacagagacacttc | o |
| 571 ttggggccgcgttctcgtctctgtacacg | o |
| 572 gagaacgctggaccttccat | s |
| 573 tccatgtcggctcctgatgct | s |
| 574 ctgtcg | s |
| 575 tcgtga | s |
| 576 cgtcga | s |
| 577 agtgct | s |
| 578 ctgtcg | o |
| 579 agtgct | o |
| 580 cgtcga | o |
| 581 tcgtga | o |
| 582 gagaacgctccagcttcgat | o |
| 583 gctagacgtaagcgtga | o |
| 584 gagaacgctcgaccttccat | o |
| 585 gagaacgctggacctatccat | o |
| 586 gctagagggttagcgtga | o |
| 587 gagaacgctggaccttccat | o |
| 588 tcacgctaacgtctagc | o |
| 589 bgctagacgttagcgtga | o |
| 590 atggaaaggtcagcgttctc | o |
| 591 gagaacgctggaccttcgat | o |
| 592 gagaacgatggaccttccat | o |
| 593 gagaacgctggaccttccat | o |
| 594 gagaacgctccagcactgat | o |
| 595 tccatgtcggctcctgctgat | o |
| 596 atgtcctcggctcctgatgct | o |
| 597 gagaacgctccaccttccat | o |
| 598 gagaacgctggaccttcgta | o |
| 599 batggaaaggtccagcgttctc | o |
| 600 tcctga | o |
| 601 tcaacgtt | o |
| 602 aacgtt | o |
| 603 aacgttga | o |
| 604 tcacgctaacctctagc | o |
| 605 gagaacgctggaccttgcat | o |
| 606 gctggaccttccat | o |
| 607 gagaacgctggacctcatccat | o |
| 608 gagaacgctggacgctcatccat | o |
| 609 aacgttgaggggcat | o |
| 610 atgccccctcaacgtt | o |
| 611 tcaacgttga | o |
| 612 gctggaccttccat | o |
| 613 caacgtt | o |
| 614 acaacgttga | o |
| 615 tcacgt | o |
| 616 tcaagctt | o |
| 617 tcgtca | o |
| 618 aggatatac | o |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|-----------------------------|----------|
| 619 tagacgtc | o |
| 620 gacgtcat | o |
| 621 ccatgcat | o |
| 622 atcgatgt | o |
| 623 atgcatgt | o |
| 624 ccatgcat | o |
| 625 agcgctga | o |
| 626 tcagcgat | o |
| 627 ccttcgat | o |
| 628 gtgccgggggtctccgggc | o |
| 629 gctgtggggcggtccctg | s |
| 630 btcaacggt | o |
| 631 ftcaacggt | o |
| 632 faacgttga | o |
| 633 tcaacgt | s |
| 634 aacgttg | s |
| 635 cgacga | o |
| 636 tcaacgtt | o |
| 637 tcgga | o |
| 638 agaacggt | o |
| 639 tcatcgat | o |
| 640 taaacggt | s |
| 641 ccaacggt | s |
| 642 gctcga | s |
| 643 cgacgt | s |
| 644 cgtcgt | s |
| 645 acgtgt | s |
| 646 cgttcg | s |
| 647 gagcaagctggaccttccat | s |
| 648 cgcgta | s |
| 649 cgtacg | s |
| 650 tcaccggt | s |
| 651 caagagatgctaacaatgca | s |
| 652 acccatcaatagctctgtgc | s |
| 653 ccacgtat | o |
| 654 tcgacgtc | o |
| 655 ctacgct | o |
| 656 taagcgt | o |
| 657 tcgcgaattcgcg | o |
| 658 atggaaaggtccagcgttct | o |
| 659 actggacggttagcgtga | o |
| 660 cgcctggggctgtctgg | o |
| 661 gtgtcgggggtctccgggc | o |
| 662 gtgccgggggtctccgggc | o |
| 663 cgcctgcgggcgggttg | o |
| 664 gaagttcacgttgaggggcat | o |
| 665 atctggtgagggcaagctatg | s |
| 666 gttgaacccgagaacatcat | s |
| 667 gcaacggt | o |
| 668 gtaacggt | o |
| 669 cgaacggt | o |
| 670 gaaacggt | o |
| 671 caaacggt | o |
| 672 ctaacggt | o |
| 673 ggaaggt | o |
| 674 tgaacggt | o |
| 675 acaacggt | o |
| 676 ttaacggt | o |
| 677 aaaacggt | o |
| 678 ataacggt | o |
| 679 aacgttct | o |
| 680 tccgatcg | o |
| 681 tccgtacg | o |
| 682 gctagacgttagcgtga | o |
| 683 gagaacgttagctcctcatccat | o |
| 684 gagaacgttagaccttctat | o |
| 685 actagacgttagtgtga | o |
| 686 cacaccttggtcaatgtcacgt | o |
| 687 tctccatctctatgggtttatcg | o |
| 688 cgttggaacttccat | o |
| 689 caccaccttggtcaatgtcacgt | o |
| 690 gctagacgttagctgga | o |
| 691 agtgcgattgcagatcg | o |
| 692 ttttcgtttgtggttttgtggtt | o |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|----------------------------|----------|
| 693 ttttcgtttgtcgttttgcgtt | |
| 694 tttttgttttgggttttgggtt | |
| 695 accgcatggattctaggcca | s |
| 696 gctagacgttagcgt | o |
| 697 aacgctggaccttccat | o |
| 698 tcaazgtt | o |
| 699 ctttcgat | o |
| 700 actagacgttagtgtga | s |
| 701 gctagaggttagcgtga | s |
| 702 atggactctccagcgttctc | o |
| 703 atcgactctcgagcgttctc | o |
| 704 gctagacgttagc | o |
| 705 gctagacgt | o |
| 706 agtgcgattcgagatcg | o |
| 707 tcagzgct | o |
| 708 ctgattgctctctcgtga | o |
| 709 tzaacgtt | o |
| 710 gagaaazgctggaccttccat | o |
| 711 gctagacgttaggctga | o |
| 712 gctacttagcgtga | o |
| 713 gctaccttagcgtga | o |
| 714 atcgactctcgagcgttctc | o |
| 715 atgcactctcgagcgttctc | o |
| 716 agtgactctccagcgttctc | o |
| 717 gccagatgttagctgga | o |
| 718 atcgactcgagcgttctc | o |
| 719 atcgatcgagcgttctc | o |
| 720 bgagaaacgctcgaccttcgat | o |
| 721 gctagacgttagcgtgga | sos |
| 722 atcgactctcgagcgttctc | sos |
| 723 tagacgttagcgtga | o |
| 724 cgactctcgagcgttctc | o |
| 725 ggggtcgaccttgagggggg | sos |
| 726 gctaacgttagcgtga | o |
| 727 cgtcgtcgt | o |
| 728 gagaa:gcaggacztccat | o |
| 729 atcgacctacgtgcgttztc | o |
| 730 atzgacctacgtgcgttctc | o |
| 731 gctagazgttagcgt | o |
| 732 atcgactctcgagzgttctc | o |
| 733 ggggtaatgcacagggggg | sos |
| 734 ggctgtattcctgactgcc | s |
| 735 ccattgtaacctctagc | o |
| 736 gctagatgttagcgtga | o |
| 737 cgtaccttacggtga | o |
| 738 tccatgctggtcctgatgct | o |
| 739 atcgactctctcgagcgttctc | o |
| 740 gctagagcttagcgtga | o |
| 741 atcgactctcgagtgttctc | o |
| 742 aacgctcgaccttcgat | o |
| 743 ctcaacgctggaccttccat | o |
| 744 atcgacctacgtgcgttctc | o |
| 745 gagaatgctggaccttccat | o |
| 746 tcacgctaacctctgac | o |
| 747 bgagaaacgctccagcactgat | o |
| 748 bgagcaagctggaccttccat | o |
| 749 cgctagaggttagcgtga | o |
| 750 gctagatgttaacgt | o |
| 751 atggaaaggtccacgttctc | o |
| 752 gctagatgttagcgt | o |
| 753 gctagacgttagtgt | o |
| 754 tccatgacggtcctgatgct | o |
| 755 tccatggcggctcctgatgct | o |
| 756 gctagacgatagcgt | o |
| 757 gctagtcgatagcgt | o |
| 758 tccatgacgttctgatgct | o |
| 759 tccatgtcgttctgatgct | o |
| 760 gctagacgttagzgt | o |
| 761 gctaggcgttagcgt | o |
| 762 tccatgtzggctcctgatgct | o |
| 763 tccatgtcggctcctgatgct | o |
| 764 atzgactctzgagzgttctc | o |
| 765 atggaaaggtccagtggttctc | o |
| 766 gcatgacgttagcgt | o |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|-----------------------------------|----------|
| 767 ggggtcaacgttgagggggg | s |
| 768 ggggtcaagctctgagggggg | sos |
| 769 cgcgcgcgcgcgcgcgcgcg | o |
| 770 cccccccccccccccccccccccc | s |
| 771 cccccccccccccccccccccccc | s |
| 772 tcaatgtcgctcctgatcct | o |
| 773 gctaaacgttagcgt | o |
| 774 tccatgtcgatcctgatgct | o |
| 775 tccatgcgggtcctgatgct | o |
| 776 aaaaatcaacgttgaaaaaaa | sos |
| 777 tccataacgttcctgatgct | o |
| 778 tggaggtcccaaccgagatcgag | o |
| 779 agtcgtcgctcgctcgctcgct | s |
| 780 ctgctgctgctgctgctgctg | s |
| 781 gagaacgctccgaccttcgat | s |
| 782 gctagatgttagcgt | s |
| 783 gcatgacgttagcgt | s |
| 784 tcaatgctgaf | o |
| 785 tcaacgttgaf | o |
| 786 tcaacgttgab | o |
| 787 gcaatattgcb | o |
| 788 gcaatattgcf | o |
| 789 agttgcaact | o |
| 790 tcttcgaa | o |
| 791 tcaacgtc | o |
| 792 ccatgtcggtcctgatgct | o |
| 793 gtttttatataatttggg | o |
| 794 tttttgtttgtcggtttgtcggt | o |
| 795 ttggggggggtt | s |
| 796 ggggttgggggtt | s |
| 797 ggtggtgtaggttttgg | o |
| 798 bgagaaazgctcgaccttgat | o |
| 799 tcaacgttaacgttaacgtt | o |
| 800 bgagcaagztggaccttccat | o |
| 801 bgagaaazgctccagcactgat | o |
| 802 tcaazgttgax | o |
| 803 gzaatattgex | o |
| 804 tgcgtctttgtcggtttgtgctt | o |
| 805 ctgcgttagcaatttaactgtg | o |
| 806 tccatgacgttcctgatgct | s |
| 807 tgcattgccgtgcacccgtacacagctct | s |
| 808 tgcattgccgtacacagctct | s |
| 809 tgcattcagctct | s |
| 810 tgcgtctct | s |
| 811 cccccccccccccccccccc | s |
| 812 cccccccccccc | s |
| 813 cccccccc | s |
| 814 tgcattcagctct | sos |
| 815 tgcattgccgtacacagctct | o |
| 816 gagcaagctggaccttccat | s |
| 817 tcaacgttaacgttaacgttaacgtt | s |
| 818 gagaacgctcgaccttcgat | s |
| 819 gtcccccattcccagaggagaaat | o |
| 820 ctgacggctgacgtcatcaagctag | o |
| 821 ctgacttgatgacgtcagccgctag | o |
| 822 cggctgacgtcatcaa | s |
| 823 ctgacgtg | o |
| 824 ctgacgtcat | o |
| 825 attcgatcgggcgggcgag | o |
| 826 ctgcggccgcccgcgacgaat | o |
| 827 gactgacgtcagcgt | o |
| 828 ctgacggctgacgtcataaagctagc | s |
| 829 ctgactttatgacgtcagccgctagc | s |
| 830 ctgacggctgagctcataaagctagc | s |
| 831 ctagtggctgacgtcatcaagctag | s |
| 832 tccaccacgtgggtctatgct | s |
| 833 gggaatgaaagattttattataag | o |
| 834 tctaaaaaccatctattcttaaccct | o |
| 835 agctcaacgtcatgc | o |
| 836 ttaacgggtgtagcggtattggtc | o |
| 837 ttaagaccaataaccgctaccaccg | o |
| 838 gatctagtgatgagtcagccggatc | o |
| 839 gatccggctgactcatcactagatc | o |
| 840 tccaagacgttcctgatgct | o |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|---|----------|
| 341 tccatgacgtccctgatgct | o |
| 342 tccaccacgtggctgatgct | o |
| 343 ccacgtggacctctagc | o |
| 344 tcagaccacgtgggtcggtgttcctga | o |
| 345 tcaggaaacaccgaccacgtggtctg ^a | o |
| 346 catttccaggatttccca | o |
| 347 ttccctctctgcaagagact | o |
| 348 tgtatctctctgaaggact | o |
| 349 ataaagcgaaaactagcagcagtttc | o |
| 350 gaaactgctgctagtttcgctttat | o |
| 351 tgcccaaaagagaaaatttgtttcatacag | o |
| 352 ctgtatgaacaaatttctctcttgggca | o |
| 353 ttagggttaggggttaggggtt | ss |
| 354 tccatgagcttccctgatgct | ss |
| 355 aaaacatgacgttcaaaaaa | ss |
| 356 aaaacatgacgttcggggggg | ss |
| 357 ggggcatgagcttcggggggg | sos |
| 358 ctaggctgacgtcatcaagctagt | o |
| 359 tctgacgtcatctgacgttggtgacgtct | o |
| 360 ggaattagtaataagatatagaagtt | o |
| 361 ttacaccttataaataactaaacaaa | o |
| 362 gcgttttttttgcg | s |
| 363 atatctaatcaaaacattataaaa | o |
| 364 tctatcccagggtggttccctgttag | o |
| 365 btccatgacgttccctgatgct | o |
| 366 btccatgagcttccctgatgct | o |
| 367 tttttttttttttf | o |
| 368 tttttttttttttf | so |
| 369 ctagcttgatgagctcagccgctag | o |
| 370 ttgagttgtcttctgcttagctaa | o |
| 371 tctatgagcttccctgagctt | s |
| 372 ctagcggctgacgtcatcaatctag | o |
| 373 tgctagctgtgctgtacct | s |
| 374 atgctaaagacgtcacattgca | o |
| 375 tgcaatgtgacgtccttttagcat | o |
| 376 gtaggggactttccgagctcgagatccctatg | o |
| 377 cataggatctcagagctcggaaagtccctac | o |
| 378 ctgtcaggaaactgcaggtaagg | o |
| 379 cataacataggaaatatttactcctcgc | o |
| 380 ctccagctccaagaaaggacg | o |
| 381 gaagtttctggtaagtcttcg | o |
| 382 tctgtcttttgtgcttttgtgctt | s |
| 383 tctgtcttttgtgcttttgtgctt | s |
| 384 tctgtcttttgtgcttttgtgctt | s |
| 385 tctgtgacgttcggcgcgcgccc | s |
| 386 tctgtgcttttgtgcttttgtgctt | s |
| 387 tccatgagcttccctgagctt | s |
| 388 tctgtcttttctgtcttttgcgctt | s |
| 389 tctgtcttttgcgtgcttctgtctt | s |
| 390 tctgtctgttttgcgttttgcgctt | s |
| 391 tctgtctgttttgcgttttgcgctt | s |
| 392 tctgtacggggaagt | s |
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| 394 tctgtgctggaagt | s |
| 395 tctgtgctggaagt | s |
| 396 tctgtgctggaagt | s |
| 397 gctgacgttcggcgcgcgccc | s |
| 398 gctgacgttcggcgcgcgccc | s |
| 399 gctgacgttcggcgcgcgccc | s |
| 400 gctgacgttcggcgcgcgccc | s |
| 401 gctgacgttcggcgcgcgccc | s |
| 402 gctgacgttcggcgcgcgccc | s |
| 403 gctgacgttcggcgcgcgccc | s |
| 404 tctgtctgtctctccg | s |
| 405 tgtgggggttttgggttttg | s |
| 406 aggggaggggaggggagggg | s |
| 407 tgtgtgtgtgtgtgtgtgtgt | s |
| 408 ctctctctctctctctctctct | chimeric |
| 409 ggggtcgcagctcgagggggg | s |
| 410 atatatatatatatatat | s |
| 411 ttttttttttttttttttttttt s | |
| 412 ttttttttttttttttttttttt | s |
| 413 ttttttttttttttttttttttt | s |
| 414 gctagaggggaggggt | |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|-----------------------------|----------|
| 915 gctagatgttagggg | |
| 916 gcatgaggggagct | |
| 917 atggaagggtccagggggctc | |
| 918 atggactctggagggggctc | |
| 919 atggaagggtccagggggctc | |
| 920 gagaaggggggaccttgga | |
| 921 gagaaggggggaccttccat | |
| 922 gagaagggggcagcactgat | |
| 923 tccatgtggggcctgatgct | |
| 924 tccatgaggggcctgatgct | |
| 925 tccatgtggggcctgatgct | |
| 926 atggactctccggggttctc | |
| 927 atggaagggtccggggttctc | |
| 928 atggactctggaggggttctc | |
| 929 atggaggtccatgggggtc | |
| 930 atggactctggggggttctc | |
| 931 tccatgtgggtggggatgct | |
| 932 tccatgcgggtggggatgct | |
| 933 tccatgggggtcctgatgct | |
| 934 tccatgggggtccctgatgct | |
| 935 tccatgggggtcctgatgct | |
| 936 tccatgggggtcctgatgct | |
| 937 tccatcgggggcctgatgct | |
| 938 gctagagggaagtgt | |
| 939 ttttttttttttttttttt | S |
| 940 gmggtcaacgttgagggmagg | S |
| 941 ggggagttctgtgaggggggg | S |
| 942 tcgtcgttttccccccccc | S |
| 943 ttgggggggttttttttttttt | S |
| 944 tttaaattttaaaatttaata | S |
| 945 ttgggttttttggttttttttg | S |
| 946 ttcccttttcccttttccctc | S |
| 947 ggggtcatcgatgagggggg s | SOS |
| 948 tccatgacgttccctgacgtt | |
| 949 tccatgacgttccctgacgtt | |
| 950 tccatgacgttccctgacgtt | |
| 951 tccatgacgttccctgacgtt | |
| 952 tccatgacgttccctgacgtt | |
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| 958 tccatgacgttccctgacgtt | |
| 959 gggggcagatcgctcggggg | SOS |
| 960 ggggtcgtacgacgggggg | SOS |
| 961 ttttttttttttttttttttt | po |
| 962 aaaaaaaaaaaaaaaaaaaaaa | po |
| 963 ccccccccccccccccccccc | po |
| 964 tcgtcgttttgctgttttgctgt | |
| 965 tcgtcgttttgctgttttgctgt | |
| 966 tcgtcgttttgctgttttgctgt | |
| 967 tcgtcgttttgctgttttgctgt | |
| 968 ggggtcaacgttgagggggg | |
| 969 ggggtcaacgttgagggggg | |
| 970 ggggtcaacgttgagggggg | |
| 971 tcgtcgttccccccccccc | |
| 972 ggggacgtcgacgtgggggg | SOS |
| 973 ggggtcgtcgacgagggggg | SOS |
| 974 ggggtcgacgtacgtcgaggggg | SOS |
| 975 ggggacgggtacgggtgggggg | SOS |
| 976 ggggtcgacgtcgagggggg | SOS |
| 977 ggggtcgacgtcgagggggg | SOS |
| 978 ggggaacgttaacgttgagggg | SOS |
| 979 ggggtcacgggtgagggggg | SOS |
| 980 ggggtcgttcgaacgagggggg | SOS |
| 981 ggggacgttcgaacgtgggggg | SOS |
| 982 tcaactttga | S |
| 983 tcaagcttga | S |
| 984 tcacgatcgtga | S |
| 985 tcacgatcgtga | S |
| 986 gggggagcatgctggggggg | SOS |
| 987 gggggggggggggggggggg | SOS |
| 988 gggggacgatatcgtcgggggg | SOS |

TABLE 1-continued

| SEQ ID NO: ODN SEQUENCE | BACKBONE |
|---|----------|
| 989 gggggacgacgtcgtcgggggg | sos |
| 990 gggggacgacgtcgtcgggggg | sos |
| 991 gggggacgtacgtcgggggg | sos |
| 992 tcaacgtt | |
| 993 tccataccgggtcctgatgct | |
| 994 tccataccgggtcctaccggt | s |
| 995 gggggacgacgttgggggg | sos |
| 996 ggggaacgacgtcgggggg | sos |
| 997 ggg ggg acg atc gtc ggg ggg | sos |
| 998 ggg gga cga tcg tcg ggg ggg | sos |
| 999 aaa gac gtt aaa | po |
| 1000 aaagagcttaaa | po |
| 1001 aaagazgttaaa | po |
| 1002 aaattgggaaa | po |
| 1003 gggggtcacgtatgagggggg | sos |
| 1004 ggggggtcaacgttggggggg | sos |
| 1005 atgtagcttaataacaaagc | po |
| 1006 ggatcccttgagttacttct | po |
| 1007 ccattccacttctgattacc | po |
| 1008 tatgtattatcatgtagata | po |
| 1009 agcctacgtattcaccctcc | po |
| 1010 ttcctgcacactactattgta | po |
| 1011 atagaaggccctacaccagt | po |
| 1012 ttacaccggtctatggagggt | po |
| 1013 ctaaccagatcaagcttagg | po |
| 1014 cctagacttgatctgggttag | po |
| 1015 tataagccctcgccgacatg | po |
| 1016 catgtcggacgaggttata | po |
| 1017 tgggtggtggggagtaagctc | po |
| 1018 gagctactcctccaccacca | po |
| 1019 gccttcgatcttctgtggga | po |
| 1020 tggacttctctttgcccgtct | po |
| 1021 atgctgtagcccagcgataa | po |
| 1022 accgaatcagcgaaagtga | po |
| 1023 tccatgacgttctgacgtt | |
| 1024 ggagaaacccatgagctcatctgg | |
| 1025 accacagaccagcaggcaga | |
| 1026 gagcgtgaactgcgcgaaga | |
| 1027 tcggtaaccttgacgaggtt | |
| 1028 ctggagccctagccaaggat | |
| 1029 gcgactccatcaccagcgat | |
| 1030 cctgaagtaagaaccagatgt | |
| 1031 ctgtgttatctgacatacacc | |
| 1032 aattagccttaggtgattggg | |
| 1033 acatctgggtcttacttcagg | |
| 1034 ataagtcataattttgggaactac | |
| 1035 cccaatcacctaaggctaatt | |
| 1036 ggggtcgtcgacgagggggg | sos |
| 1037 ggggtcgttcgaacgagggggg | sos |
| 1038 ggggacgttcgaacgtgggggg | sos |
| 1039 tcctggcgggaaagt | s |
| 1040 ggggaacgacgtcgttgggggg | sos |
| 1041 ggggaacgtacgtcgggggg | sos |
| 1042 ggggaacgtacgtacgttgggggg | sos |
| 1043 ggggtcaccggtgagggggg | sos |
| 1044 ggggtcgacgtacgtcagggggg | sos |
| 1045 ggggaccggtaccggtgggggg | sos |
| 1046 gggtcgacgtcaggggggg | sos |
| 1047 ggggtcgacgtcagggggg | sos |
| 1048 ggggaacgttaacgttgggggg | sos |
| 1049 ggggacgtcgacgtgggggg | sos |
| 1050 gcactcttcgaagctacagccggcagcctctgat | |
| 1051 cggctcttccatgaggtctttgctaatcttgg | |
| 1052 cggctcttccatgaaagcttttgacgatgtgagc | |
| 1053 tcctgcaggttaagt | s |
| 1054 gggggtcgttcgttggggggg | sos |
| 1055 gggggatgattgttggggggg | sos |
| 1056 gggggazgatzgttggggggg | sos |
| 1057 gggggagctagcttggggggg | sos |
| 1058 ggttcttttgggtccttgtct | s |
| 1059 ggttcttttgggtccttgtct | s |
| 1060 ggttcttttgggtccttgtct | s |
| 1061 ggttcttttgggtccttgtct | s |
| 1062 tgggtcttttgggtccttgtct | s |

TABLE 1-continued

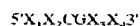
| SEQ ID NO: | ODN SEQUENCE | BACKBONE |
|------------|-----------------------------|----------|
| 1063 | gggtcaaatggtctctgtct | S |
| 1064 | gggtcttttggcgctgtct | S |
| 1065 | tccaggactctctcaggttttt | S |
| 1066 | tccaaaaactctctcaaat | S |
| 1067 | tactacttttatactttatactt | S |
| 1068 | tgtgtgtgtgtgtgtgtgtgtgt | S |
| 1069 | ttgttgtgtgtgtgtgtgtgtgtgt | S |
| 1070 | ggctccggggagggaattttgtctat | S |
| 1071 | gggacgatcgtcggggggg | SOS |
| 1072 | gggtcgtcgacgagggggg | SOS |
| 1073 | ggtcgtcgacgagggggg | SOS |
| 1074 | gggtcgtcgtcgtggggggg | SOS |
| 1075 | ggggacgatcgtcggggggg | SOS |
| 1076 | ggggacgtcgtcgtggggggg | SOS |
| 1077 | ggggtcgacgtcgacgtcgaggggggg | SOS |
| 1078 | ggggaaccgcggttggggggg | SOS |
| 1079 | ggggacgacgtcgtggggggg | SOS |
| 1080 | tcgtcgtcgtcgtcgtggggggg | SOS |
| 1081 | tcctgccgggggaagt | S |
| 1082 | tcctgcaagggaagt | S |
| 1083 | tcctgaagggaagt | S |
| 1084 | tcctggcggggaagt | S |
| 1085 | tcctggcggggaagt | S |
| 1086 | tcctggcggggaagt | S |
| 1087 | tcggggcggggaagt | S |
| 1088 | tcggggcggggaagt | S |
| 1089 | tcggggcggggaagt | S |
| 1090 | gggggacgttggggg | S |
| 1091 | ggggttttttttttgggggg | SOS |
| 1092 | ggggccccccccgggggg | SOS |
| 1093 | ggggttgttgttgtggggg | SOS |

[0053] In some embodiments, the immunostimulatory nucleic acid is a CpG nucleic acid. CpG sequences, while relatively rare in human DNA are commonly found in the DNA of infectious organisms such as bacteria. The human immune system has apparently evolved to recognize CpG sequences as an early warning sign of infection and to initiate an immediate and powerful immune response against invading pathogens without causing adverse reactions frequently seen with other immune stimulatory agents. Thus CpG containing nucleic acids, relying on this innate immune defense mechanism can utilize a unique and natural pathway for immune therapy. The effects of CpG nucleic acids on immune modulation have been described extensively in published patent applications, such as PCT US95/01570), PCT/US97/19791, PCT/US98/03678; PCT/US98/10408; PCT/US98/04703; PCT/US99/07335; and PCT/US99/09863. The entire contents of each of these patent applications is hereby incorporated by reference.

[0054] A CpG nucleic acid is a nucleic acid which includes at least one unmethylated CpG dinucleotide. A nucleic acid containing at least one unmethylated CpG dinucleotide is a nucleic acid molecule which contains an unmethylated cytosine in a cytosine-guanine dinucleotide sequence (i.e. "CpG DNA" or DNA containing a 5' cytosine followed by 3' guanosine and linked by a phosphate bond) and activates the immune system. The CpG nucleic acids can be double-stranded or single-stranded. Generally, double-stranded molecules are more stable in vivo, while single-stranded molecules have increased immune activity. Thus in some aspects of the invention it is preferred that the nucleic acid be single stranded and in other aspects it is preferred that the nucleic acid be double stranded. The terms

CpG nucleic acid or CpG oligonucleotide as used herein refer to an immunostimulatory CpG nucleic acid or a nucleic acid unless otherwise indicated. The entire immunostimulatory nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5' CG 3' must be unmethylated.

[0055] In one preferred embodiment the invention provides an immunostimulatory nucleic acid which is a CpG nucleic acid represented by at least the formula:



[0056] wherein X₁, X₂, X₃, and X₄ are nucleotides. In one embodiment X₂ is adenine, guanine, cytosine, or thymine. In another embodiment X₃ is cytosine, guanine, adenine, or thymine. In other embodiments X₂ is adenine, guanine, or thymine and X₃ is cytosine, adenine, or thymine.

[0057] In another embodiment the immunostimulatory nucleic acid is an isolated CpG nucleic acid represented by at least the formula:



[0058] wherein X_1, X_2, X_3 , and X_4 are nucleotides and N is any nucleotide and N_1 and N_2 are nucleic acid sequences composed of from about 0-25 N 's each. In one embodiment X_1X_2 are nucleotides selected from the group consisting of: CpT, GpG, GpA, ApA, ApT, ApG, CpT, CpA, CpG, TpA, TpT, and TpG; and X_3X_4 are nucleotides selected from the group consisting of: TpT, ApT, TpG, ApG, CpG, TpC, ApC, CpC, TpA, ApA, and CpA. Preferably X_1X_2 are GpA or GpT and X_3X_4 are TpT. In other embodiments X_1 or X_2 or both are purines and X_3 or X_4 or both are pyrimidines or X_1X_2 are GpA and X_3 or X_4 or both are pyrimidines. In another

not exclusively associated with atopic or allergic symptoms. An "initiator" as used herein refers to a composition or environmental condition which triggers asthma. Initiators include, but are not limited to, allergens, cold temperatures, exercise, viral infections, SO₂.

[0103] In another aspect the invention provides methods for treating or preventing asthma or allergy in a hypo-responsive subject. As used herein, a hypo-responsive subject is one who has previously failed to respond to a treatment directed at treating or preventing asthma or allergy or one who is at risk of not responding to such a treatment. The treatment directed at treating or preventing asthma or allergy may be an asthma/allergy medicament, in which case the hypo-responsive subject is one who is hypo-responsive to an asthma/allergy medicament.

[0104] Other subjects who are hypo-responsive include those who are refractory to an asthma/allergy medicament. As used herein, the term "refractory" means resistant or failure to yield to treatment. Such subjects may be those who never responded to an asthma/allergy medicament (i.e., subjects who are non-responders), or alternatively, they may be those who at one time responded to an asthma/allergy medicament, but have since that time have become refractory to the medicament. In some embodiments, the subject is one who is refractory to a subset of medicaments. A subset of medicaments is at least one medicament. In some embodiments, a subset refers to 2, 3, 4, 5, 6, 7, 8, 9, or 10 medicaments.

[0105] In other embodiments, hypo-responsive subjects are elderly subjects, regardless of whether they have or have not previously responded to a treatment directed at treating or preventing asthma or allergy. Elderly subjects, even those who have previously responded to such treatment, are considered to be at risk of not responding to a future administration of this treatment. Similarly, neonatal subjects are also considered to be at risk of not responding to treatment directed at treating or preventing asthma or allergy.

[0106] In some embodiments, an immunostimulatory nucleic acid is administered to the hypo-responsive subject without the further administration of an asthma/allergy medicament. In yet other embodiments, an asthma/allergy medicament is administered to the hypo-responsive subject, in which case it may be administered substantially simultaneously (i.e., concurrently) with, or following the administration of the immunostimulatory nucleic acid.

[0107] An "asthma/allergy medicament" as used herein is a composition of matter which reduces the symptoms, inhibits the asthmatic or allergic reaction, or prevents the development of an allergic or asthmatic reaction. Various types of medicaments for the treatment of asthma and allergy are described in the Guidelines For The Diagnosis and Management of Asthma, Expert Panel Report 2, NIH Publication No. 97/4051, Jul. 19, 1997, the entire contents of which are incorporated herein by reference. The summary of the medicaments as described in the NIH publication is presented below.

[0108] In most embodiments the asthma/allergy medicament is useful to some degree for treating both asthma and allergy. Some asthma/allergy medicaments are preferably used in combination with the immunostimulatory nucleic acids to treat asthma. These are referred to as asthma

medicaments. Asthma medicaments include, but are not limited, PDE-4 inhibitors, bronchodilator/beta-2 agonists, K⁺ channel openers, VLA-4 antagonists, neurokin antagonists, TXA₂ synthesis inhibitors, xanthanines, arachidonic acid antagonists, 5 lipoxygenase inhibitors, thromboxin A₂ receptor antagonists, thromboxane A₂ antagonists, inhibitor of 5-lipoxygenase activation proteins, and protease inhibitors.

[0109] Bronchodilator/beta-2 agonists are a class of compounds which cause bronchodilation or smooth muscle relaxation. Bronchodilator/beta-2 agonists include, but are not limited to, salmeterol, salbutamol, albuterol, terbutaline, D2522/formoterol, fenoterol, bitolterol, pirbuterol methylxanthines and orciprenaline. Long-acting β_2 agonists and bronchodilators which are used for long-term prevention of symptoms in addition to the anti-inflammatory therapies. They function by causing bronchodilation, or smooth muscle relaxation, following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction. These compounds also inhibit mast cell mediator release, decrease vascular permeability and increase mucociliary clearance. Long-acting β_2 agonists include, but are not limited to, salmeterol and albuterol. These compounds are usually used in combination with corticosteroids and generally are not used without any inflammatory therapy. They have been associated with side effects such as tachycardia, skeletal muscle tremor, hypokalemia, and prolongation of QTc interval in overdose.

[0110] Methylxanthines, including for instance theophylline, have been used for long-term control and prevention of symptoms. These compounds cause bronchodilation resulting from phosphodiesterase inhibition and likely adenosine antagonism. It is also believed that these compounds may effect eosinophilic infiltration into bronchial mucosa and decrease T-lymphocyte numbers in the epithelium. Dose-related acute toxicities are a particular problem with these types of compounds. As a result, routine serum concentration must be monitored in order to account for the toxicity and narrow therapeutic range arising from individual differences in metabolic clearance. Side effects include tachycardia, nausea and vomiting, tachyarrhythmias, central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia and hypokalemia. Short-acting β_2 agonists/bronchodilators relax airway smooth muscle, causing the increase in air flow. These types of compounds are a preferred drug for the treatment of acute asthmatic systems. Previously, short-acting β_2 agonists had been prescribed on a regularly-scheduled basis in order to improve overall asthma symptoms. Later reports, however, suggested that regular use of this class of drugs produced significant diminution in asthma control and pulmonary function (Sears, et al. *Lancet*; 336:1391-6, 1990). Other studies showed that regular use of some types of β_2 agonists produced no harmful effects over a four-month period but also produced no demonstrable effects (Drazen, et al., *N. Eng. J. Med.*; 335:841-7, 1996). As a result of these studies, the daily use of short-acting β_2 agonists is not generally recommended. Short-acting β_2 agonists include, but are not limited to, albuterol, bitolterol, pirbuterol, and terbutaline. Some of the adverse effects associated with the administration of short-acting β_2 agonists include tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, and hyperglycemia.

agents such as adjuvants to enhance immune responses even further. The immunostimulatory nucleic acid, asthma/allergy medicament and other therapeutic agent may be administered simultaneously or sequentially. When the other therapeutic agents are administered simultaneously they can be administered in the same or separate formulations, but are administered at the same time. The other therapeutic agents are administered sequentially with one another and with the immunostimulatory nucleic acid and asthma/allergy medicament, when the administration of the other therapeutic agents and the immunostimulatory nucleic acid and asthma/allergy medicament is temporally separated. The separation in time between the administration of these compounds may be a matter of minutes or it may be longer. Other therapeutic agents include but are not limited to non-nucleic acid adjuvants, cytokines, antibodies, antigens, etc.

[0160] A "non-nucleic acid adjuvant" is any molecule or compound except for the immunostimulatory nucleic acids described herein which can stimulate the humoral and/or cellular immune response. Non-nucleic acid adjuvants include, for instance, adjuvants that create a depo effect, immune stimulating adjuvants, adjuvants that create a depo effect and stimulate the immune system and mucosal adjuvants.

[0161] An "adjuvant that creates a depo effect" as used herein is an adjuvant that causes an antigen or allergen to be slowly released in the body, thus prolonging the exposure of immune cells to the antigen or allergen. This class of adjuvants includes but is not limited to alum (e.g., aluminum hydroxide, aluminum phosphate); or emulsion-based formulations including mineral oil, non-mineral oil, water-in-oil or oil-in-water-in oil emulsion, oil-in-water emulsions such as Seppic ISA series of Montanide adjuvants (e.g., Montanide ISA 720, AirLiquide, Paris, France); MF-59 (a squalene-in-water emulsion stabilized with Span 85 and Tween 80; Chiron Corporation, Emeryville, Calif.; and PROVAX (an oil-in-water emulsion containing a stabilizing detergent and a micelle-forming agent; IDEC, Pharmaceuticals Corporation, San Diego, Calif.).

[0162] An "immune stimulating adjuvant" is an adjuvant that causes activation of a cell of the immune system. It may, for instance, cause an immune cell to produce and secrete cytokines. This class of adjuvants includes but is not limited to saponins purified from the bark of the *Q. saponaria* tree, such as QS21 (a glycolipid that elutes in the 21st peak with HPLC fractionation; Aquila Biopharmaceuticals, Inc., Worcester, Mass.); poly[di(carboxylatophenoxy)phosphazene (PCPP polymer; Virus Research Institute, USA); derivatives of lipopolysaccharides such as monophosphoryl lipid A (MPL; Ribi ImmunoChem Research, Inc., Hamilton, Mont.), muramyl dipeptide (MDP; Ribi) and threonyl-muramyl dipeptide (t-MDP; Ribi); OM-174 (a glucosamine disaccharide related to lipid A; OM Pharma SA, Meyrin, Switzerland); and Leishmania elongation factor (a purified Leishmania protein; Corixa Corporation, Seattle, Wash.).

[0163] "Adjuvants that create a depo effect and stimulate the immune system" are those compounds which have both of the above-identified functions. This class of adjuvants includes but is not limited to ISCOMS (Immunostimulating complexes which contain mixed saponins, lipids and form virus-sized particles with pores that can hold antigen; CSL, Melbourne, Australia); SB-AS2 (SmithKline Beecham adju-

vant system #2 which is an oil-in-water emulsion containing MPL and QS21; SmithKline Beecham Biologicals [SBB], Rixensart, Belgium); SB-AS4 (SmithKline Beecham adjuvant system #4 which contains alum and MPL; SBB, Belgium); non-ionic block copolymers that form micelles such as CRL 1005 (these contain a linear chain of hydrophobic polyoxpropylene flanked by chains of polyoxyethylene; Vaxcel, Inc., Norcross, Ga.); and Syntex Adjuvant Formulation (SAF, an oil-in-water emulsion containing Tween 80 and a nonionic block copolymer; Syntex Chemicals, Inc., Boulder, Colo.).

[0164] A "non-nucleic acid mucosal adjuvant" as used herein is an adjuvant other than an immunostimulatory nucleic acid that is capable of inducing a mucosal immune response in a subject when administered to a mucosal surface in conjunction with an antigen or allergen. Mucosal adjuvants include but are not limited to Bacterial toxins: e.g., Cholera toxin (CT), CT derivatives including but not limited to CT B subunit (CTB) (Wu et al., 1998, Tochikubo et al., 1998); CTD53 (Val to Asp) (Fontana et al., 1995); CTK97 (Val to Lys) (Fontana et al., 1995); CTK104 (Tyr to Lys) (Fontana et al., 1995); CTD53/K63 (Val to Asp, Ser to Lys) (Fontana et al., 1995); CTH54 (Arg to His) (Fontana et al., 1995); CTN107 (His to Asn) (Fontana et al., 1995); CTE114 (Ser to Glu) (Fontana et al., 1995); CTE112K (Glu to Lys) (Yamamoto et al., 1997a); CTS61F (Ser to Phe) (Yamamoto et al., 1997a, 1997b); CTS106 (Pro to Lys) (Douce et al., 1997, Fontana et al., 1995); and CTK63 (Ser to Lys) (Douce et al., 1997, Fontana et al., 1995), Zonula occludens toxin, zot, *Escherichia coli* heat-labile enterotoxin, Labile Toxin (LT), LT derivatives including but not limited to LT B subunit (LTB) (Verweij et al., 1998); LT7K (Arg to Lys) (Komase et al., 1998, Douce et al., 1995); LT61F (Ser to Phe) (Komase et al., 1998); LT112K (Glu to Lys) (Komase et al., 1998); LT118E (Gly to Glu) (Komase et al., 1998); LT146E (Arg to Glu) (Komase et al., 1998); LT192G (Arg to Gly) (Komase et al., 1998); LTK63 (Ser to Lys) (Marchetti et al., 1998, Douce et al., 1997, 1998, Di Tommaso et al., 1996); and LTR72 (Ala to Arg) (Giuliani et al., 1998), Pertussis toxin, PT. (Lycke et al., 1992, Spangler BD, 1992, Freytag and Clements, 1999, Roberts et al., 1995, Wilson et al., 1995) including PT-9K/129G (Roberts et al., 1995, Cropley et al., 1995); Toxin derivatives (see below) (Holmgren et al., 1993, Verweij et al., 1998, Rappuoli et al., 1995, Freytag and Clements, 1999); Lipid A derivatives (e.g., monophosphoryl lipid A, MPL) (Sasaki et al., 1998, Vancott et al., 1998; Muramyl Dipeptide (MDP) derivatives (Fukushima et al., 1996, Ogawa et al., 1989, Michalek et al., 1983, Morisaki et al., 1983); Bacterial outer membrane proteins (e.g., outer surface protein A (OspA) lipoprotein of *Borrelia burgdorferi*, outer membrane protein of *Neisseria meningitidis*) (Marinero et al., 1999, Van de Verg et al., 1996); Oil-in-water emulsions (e.g., MF59) (Barchfield et al., 1999, Verschoor et al., 1999, O'Hagan, 1998); Aluminum salts (Isaka et al., 1998, 1999); and Saponins (e.g., QS21) Aquila Biopharmaceuticals, Inc., Worcester, Mass.) (Sasaki et al., 1998, MacNeal et al., 1998), ISCOMS, MF-59 (a squalene-in-water emulsion stabilized with Span 85 and Tween 80; Chiron Corporation, Emeryville, Calif.); the Seppic ISA series of Montanide adjuvants (e.g., Montanide ISA 720; AirLiquide, Paris, France); PROVAX (an oil-in-water emulsion containing a stabilizing detergent and a micelle-forming agent; IDEC Pharmaceuticals Corporation, San Diego, Calif.); Syntex Adjuvant Formulation (SAF;

Syntex Chemicals, Inc., Boulder, Colo.); poly[di(carboxylatophenoxy)phosphazene (PCPP polymer; Virus Research Institute, USA) and Leishmania clonogenic factor (Corixa Corporation, Seattle, Wash.).

[0165] Immune responses can also be induced or augmented by the co-administration or co-linear expression of cytokines (Bueller & Mulligan, 1996; Chow et al., 1997; Geissler et al., 1997; Iwasaki et al., 1997; Kim et al., 1997) or B-7 co-stimulatory molecules (Iwasaki et al., 1997; Tsuji et al., 1997) with the immunostimulatory nucleic acids and asthma/allergy medicaments. The cytokines can be administered directly with immunostimulatory nucleic acids or may be administered in the form of a nucleic acid vector that encodes the cytokine, such that the cytokine can be expressed *in vivo*. In one embodiment, the cytokine is administered in the form of a plasmid expression vector. The term "cytokine" is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment. Examples of cytokines include, but are not limited to IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-15, IL-18, granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), interferon- γ (IFN- γ), IFN- α , tumor necrosis factor (TNF), TGF- β , FLT-3 ligand, and CD40 ligand. Cytokines play a role in directing the T cell response. Helper (CD4+) T cells orchestrate the immune response of mammals through production of soluble factors that act on other immune system cells, including other T cells. Most mature CD4+ T helper cells express one of two cytokine profiles: Th1 or Th2. In some embodiments it is preferred that the cytokine be a Th1 cytokine.

[0166] The term "effective amount" of an immunostimulatory nucleic acid and an asthma/allergy medicament refers to the amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of an immunostimulatory nucleic acid and an asthma/allergy medicament for treating or preventing asthma or preventing is that amount necessary to prevent the development of IgE in response to an allergen or initiator upon exposure to the allergen or initiator is that amount necessary to cause the shift from Th2 to Th1 response in response to an allergen or initiator.

[0167] Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular immunostimulatory nucleic acid or asthma/allergy medicament being administered (e.g. the type of nucleic acid, i.e. a CpG nucleic acid, the number of unmethylated CpG motifs or their location in the nucleic acid, the degree of modification of the backbone to the oligonucleotide the type of medicament), the size of the subject, or the severity of the disease

or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular immunostimulatory nucleic acid and/or asthma/allergy medicament and/or other therapeutic agent without necessitating undue experimentation.

[0168] Depending upon the aspect of the invention, the immunostimulatory nucleic acid and asthma/allergy medicament may be administered in a synergistic amount effective to treat or prevent asthma or allergy. A synergistic amount is that amount which produces a physiological response that is greater than the sum of the individual effects of either the immunostimulatory nucleic acid or the asthma/allergy medicament alone. For instance, in some embodiments of the invention, the physiological effect is a reduction in IgE levels. A synergistic amount is that amount which produces a reduction in IgE that is greater than the sum of the IgE reduced by either the immunostimulatory nucleic acid or the asthma/allergy medicament alone. In other embodiments, the physiological result is a shift from Th2 cytokines, such as IL-4 and IL-5, to Th1 cytokines, such as IFN- γ and IL-12. The synergistic amount in this case is that amount which produces the shift to a Th1 cytokine that is greater than the sum of the shift produced by either the immunostimulatory nucleic acid or the asthma/allergy medicament alone. In other embodiments the physiological result is a decrease in eosinophilia, hyperactivity, or lung function.

[0169] In some embodiments of the invention, the immunostimulatory nucleic acid is administered in an effective amount for preventing bacterial or viral infection. Immunostimulatory nucleic acids are known to be useful for preventing bacterial and viral infections. Bacterial and viral infections exacerbate and/or induce allergy and/or asthma. In this aspect of the invention, the immunostimulatory nucleic acid is administered to the subject in an amount effective to prevent bacterial and viral infection and the asthma/allergy medicament is administered to the subject when symptoms of allergy or asthma appear. Thus, the immunostimulatory nucleic acid is administered to the subject and then the asthma/allergy medicament is subsequently administered to the subject or they are administered together at the same time. This method is particularly useful in subjects such as children and immunocompromised subjects, or elderly subjects, who are particularly susceptible to bacterial or viral disease.

[0170] In aspects of the invention directed at treating subjects in anticipation of an asthmatic or allergic event or season (e.g., in anticipation of the hay-fever season), the subjects may be administered an immunostimulatory nucleic acid in an effective amount for preventing the asthma or allergy. In related embodiments of this method, an asthma/allergy medicament is also administered to the subject. In these latter instances, the amount of the immunostimulatory nucleic acid administered may be that amount necessary to reduce the effective dose of the asthma/allergy medicament which is required to treat or prevent the asthma or allergy.

[0171] Thus, in these embodiments, the immunostimulatory nucleic acid potentiates the effect of the asthma/allergy medicament. The ability to potentiate the effect of an asthma/allergy medicament is useful since it allows for a reduction in the administered dose of an asthma/allergy medicament with the same or better therapeutic result. As an